

1 **Functional Electrical Stimulation for foot drop in Multiple Sclerosis: A**
2 **Systematic Review and Meta-Analysis of the impact on gait speed.**

3 Miller L, MPhil^{1, 2}, McFadyen A, PhD³ , Lord AC, MSc¹, Hunter R, BSc¹,
4 Paul L, PhD⁴, Rafferty D², Bowers R⁵, Mattison P¹

5
6 Affiliations: 1MS service, NHS Ayrshire and Arran, Scotland ,UK ; 2 School of
7 Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK; 3 AKM
8 Statistics, Glasgow, UK; 4 School of Medicine, Glasgow University, Glasgow,
9 UK; 5 Department of Biomedical Engineering, Strathclyde University, Glasgow,
10 UK

11
12 Corresponding author: L Miller, Douglas Grant Rehabilitation Centre, Ayrshire
13 Central Hospital, Irvine, UK,KA12 8SS. Tel:01294 323057 email:
14 linda.renfrew@aapct.scot.nhs.uk

15

16 **Acknowledgements**

17 No acknowledgements

18 **Conflicts of Interests**

19 There are no conflicts of interest to declare

20

21 **Abstract**

22 **Objective:** To review the efficacy of functional electrical stimulation (FES) used for foot drop in people with multiple sclerosis
23 (pwMS) on gait speed in short and long walking performance tests.

24 **Data sources:** Five databases (Cochrane Library, CINAHL, Embase, MEDLINE, Pubmed) and reference lists were searched.

25 **Study selection:** Studies of both observational and experimental design where gait speed data in pwMS could be extracted were
26 included.

27 **Data extraction:** Data were independently extracted and recorded. Methodological quality was assessed using the Effective Public
28 Health Practice Project (EPHPP) tool.

29 **Data synthesis:** Nineteen studies (described in 20 articles) recruiting 490 pwMS were identified and rated moderate or weak, with
30 none gaining a strong rating. All studies rated weak for blinding. Initial and ongoing orthotic and therapeutic effects were assessed

31 with regards to the impact of FES on gait speed in short and long walking tests. Meta-analyses of the short walk tests revealed a
32 significant initial orthotic effect ($t = 2.14$, $p = 0.016$) with a mean increase in gait speed of 0.05 meters per second (m/s) and
33 ongoing orthotic effect ($t = 2.81$, $p = 0.003$) with a mean increase of 0.08m/s. There were no initial or ongoing effect on gait speed
34 in long walk tests and no therapeutic effect on gait speed in either short or long walk tests.

35 **Conclusions:** FES used for foot drop has a positive initial and ongoing effect on gait speed in short walking tests. Further fully-
36 powered randomized controlled trials comparing FES with alternative treatments are required.

37
38 **Key words:** Review, Multiple Sclerosis, electric stimulation, gait disorders/neurologic, walking

39
40 **Abbreviations:**

41 **AFO** Ankle Foot Orthosis

42 **EPHPP** Effective Public Health Practice Project

43 **FES** Functional Electrical Stimulation

44 **m/s** meters per second

45 **MS** Multiple Sclerosis

46 **NICE** National Institute for Health and Care Excellence

47 **ODFS** Odstock Dropped Foot stimulator

48 **pwMS** people with Multiple Sclerosis

49 **RCT** Randomized Controlled trial

50 **UK** United Kingdom

51 **USA** United States of America

52 **10MWT** 10 meter walk test

53 **6MWT** 6 meter walkway test

54 **25ftWT** 25 foot walk test

55 **2minWT** 2 minute walk test

56 **3minWT** 3 minute walk test

57 **4minWT** 4 minute walk test

58 **5minSSWS** 5 minute self selected walk speed

59 **6minWT** 6 minute walk test

60

61

62

63

64 **Introduction**

65 Multiple Sclerosis (MS), a chronic autoimmune demyelinating central nervous system disease, is the leading cause of disability in
66 young adults in Western Europe and North America¹⁻⁴. In 2010, there were an estimated 130,000 cases of MS in the UK, with an
67 incidence of 11.52 per 100,000 in women and 4.84 per 100,000 in men⁴.

68 MS is a progressive disease with accumulation of irreversible neurological deficits, and is characterised by visual, brainstem,
69 cerebellar, cognitive, motor and sensory symptoms^{1, 2}. Ambulatory impairment is the main contributor to disability within the first 10
70 years⁵ with around 75% of people with MS reporting limitations in walking⁶. Timed walking tests provide a quantitative measure of
71 walking performance, which have demonstrated good reliability in pwMS⁷ and are strongly associated with self-reported walking
72 ability⁶. Habitual walking performance, described as the number of steps taken in an individual's own environment (accelerometry)
73 is predicted by gait speed as measured by a range of walking speed performance tests, making it a valid outcome in interventional
74 studies⁸. Walking capacity tests encompass measures of both short (e.g. 10 meter walk test (10MWT)) and longer (e.g. 6 minute
75 walk test (6minWT)) timed measures of walking⁹. Short and long walking tests have been found to indicate distinct aspects of
76 walking. Short walk tests are accurate descriptors of walking capacity and longer walking tests are recommended in interventional
77 studies⁹.

78 The inability to maintain active ankle dorsiflexion during the swing phase of the gait cycle results in foot drop, impacting on the
79 energy cost and speed of walking⁶, instability and falls¹⁰. FES is an assistive technology used for foot drop in MS and other
80 neurological conditions. FES was initially developed for use during gait in 1960 by Liberson et al.¹¹ who demonstrated immediate
81 benefits on walking in hemiplegic patients. Previous studies have reported effects of FES on gait in people with MS (pwMS) with
82 reference to walking speed and energy cost^{12,13}. The effects of FES are commonly described in terms of orthotic effects and
83 therapeutic effects. An orthotic effect, most frequently reported, refers to the difference in performance between walking with and
84 without FES. An initial orthotic effect is the immediate change seen with FES on the first day of its use¹². An ongoing orthotic effect
85 is the change in walking with and without FES at a follow up point following a period of regular use¹². The therapeutic effect
86 describes the impact of regular use of FES on walking performance over time and is the difference in walking performance without
87 FES prior to application compared to a follow up assessment without the device¹².

88 There are a number of commercially available FES devices for clinical application. They all apply electrical stimulation to the
89 common peroneal nerve, activating ankle dorsiflexion during the swing phase of gait and assisting foot clearance. Stimulation is
90 synchronised with the gait cycle using a variety of mechanisms employed by the devices including tilt sensors, heel switches, and
91 wired and wireless technology. Stimulation can be applied externally via surface electrodes or internally via implantable electrodes.
92 Recent research suggests that implantable devices are as effective as surface stimulation alternatives for pwMS¹³, although there
93 are additional risks such as device failure and neuropraxia¹³.

94 A recent narrative review¹⁴ described the impact of FES in MS on the speed, kinematic profile and energy cost of walking and with
95 regards to patient satisfaction and perceived benefits of FES. The review found FES to have beneficial orthotic and training effects
96 on measures of gait, however not all improvements were statistically or clinically significant. Although the majority of patient
97 reported data demonstrated positive benefits with FES, there was often no correlation with objective measures of gait. The authors
98 highlighted areas for further research including comparisons with usual care, e.g. an Ankle-Foot Orthosis (AFO), in addition to
99 measuring longer term effects and identifying predictors of FES response. A previous systematic review in chronic stroke found
100 orthotic effects of FES on the speed and physiological cost of walking¹⁵. One review undertaking meta-analysis noted significant
101 orthotic effect on the 10mWT¹⁶ and another noted a therapeutic effect on the 6minWT¹⁷ using FES for foot drop in stroke. There are
102 clear differences however between stroke and MS, an autoimmune neurodegenerative disease, with regards to their pathology and
103 demographic profile that may impact on the effectiveness of FES. There is a growing body of evidence for FES for foot drop in MS,
104 therefore there is a need for a systematic review to explore the efficacy of the intervention. Thus, the aim was to systematically
105 review the evidence to date for the orthotic and therapeutic effects of surface and implantable FES used for foot drop in pwMS, with
106 regards to its impact on gait speed in both short and long walking performance tests.

107

108 **Materials and methods**

109 A literature search was conducted on 27th September 2016 by two authors (AS, RH) using a protocol developed a priori.

110 Due to the limited number of known controlled trials in this field of study the review was purposefully inclusive, including empirical
111 research and studies of both observational and experimental design evaluating FES as an intervention. Opinion pieces, narrative
112 reviews, conference and poster abstracts, and studies not in the English language were excluded. No restrictions were place on
113 publication date.

114 Studies on adult participants (>18 years) with a diagnosis of MS were included. Studies investigating a mixed neurological sample
115 were included where data for pwMS could be extracted separately.

116 Studies included all types of FES devices for foot drop. Studies investigating other interventions in addition to FES were included
117 where the other intervention was a comparator group. Studies reporting on device development were excluded.

118 To be eligible for inclusion studies had to report on a minimum of one measure of gait speed using either short or long walking tests
119 with and without the device, at a minimum of one time point. Gait speed is described in meters per second (m/s) and measured by
120 walking over a short distance (e.g. 10 meters, 25 feet) or a longer distance (e.g. 2 or 6 Minute Walk)

121 Search strategy

122 The following databases were searched: CINAHL via EBSCO, Embase and Medline via OVID, the Cochrane library and PubMed
123 that included in-process citations. Individual search strategies were conducted in each database using the key search terms,

124 Medical Subject Headings and Boolean operators shown in Table 1 and applying the previously agreed eligibility criteria. A hand
125 search of the reference lists of relevant articles was undertaken.

126 The search results were exported from the individual database to a specialised referencing software package (REFWORKS) and
127 duplicates were removed. Articles were screened by title (AS) and the abstracts were reviewed by two authors (AS, RH). In the
128 case of disagreement over inclusion at abstract review stage, consensus was reached by consulting a third reviewer (LR). The full
129 text of articles that met inclusion/exclusion criteria were read and assessed for eligibility.

130 [Insert table 1 here]

131 Quality assessment

132 There is no 'gold standard' critical appraisal tool recommended in rehabilitation research, however a systematic review of available
133 critical appraisal tools recommends tools should be selected based on the purpose of the review¹⁸. The Effective Public Health
134 Practice Project (EPHPP) tool¹⁹ was selected following consideration of the research question and recommendations from previous
135 systematic reviews^{20, 21}. The EPHPP tool provides a checklist with a summary score that allows for inclusion of a range of different
136 study designs within the review. The EPHPP tool has demonstrated good reliability and validity²⁰.

137 The articles for review were initially identified as either observational or experimental in design using the Scottish Intercollegiate
138 Guidelines Network algorithm for study design (Figure 1). A pilot quality check was undertaken on one article by all 4 assessors

139 (LR, LP, AS, RH) to ensure consistency. Subsequently 2 reviewers reviewed each article and where there were discrepancies an
140 agreement was reached via discussion.

141 Data extraction and analysis

142 One reviewer (LR) extracted data from the articles on participants (e.g. age, gender, MS type), methods (e.g. study design)
143 interventions (FES type, description of control intervention) and outcomes (e.g. assessment time points and outcome measures)
144 and results using an a priori developed data extraction form. A second reviewer (AS) checked the data extracted. Authors were
145 contacted where further clarification was required around data.

146 Data, where available, were subjected to meta-analysis as per Everitt²². Data from all 3 short walking tests (10MWT, 25 foot walk
147 test (25ftWT), 6 meter walkway test (6MWT)) were combined and presented as the primary outcome measure. Data from all the
148 longer walking tests (2 minute walk test (2minWT), 3 minute walk test (3minWT), 4 minute walk test (4minWT), 6minWT, 5 minute
149 self-selected walk test (5minSSWS)) were combined and presented as the secondary outcome measure. Justification for combining
150 data from the longer walking tests was based on previous evidence that noted a strong association between the 2minWT and
151 6minWT in pwMS²³. Initial and continued orthotic and therapeutic effects of FES were analysed. Given the differences in protocol
152 timings in each study included in the meta-analysis calculations and the lack of randomness, a heuristic approach was taken as no
153 Odds Ratios were reported. This approach has been previously used in other clinical areas²⁴. All calculations are from baseline

154 data given the differences in times between study protocols and, where only sample size, means and standard deviations were
155 reported, 95% confidence intervals were estimated with the assumption of approximate Normal distributions. The estimates of the
156 95% confidence intervals of the mean of each outcome variable from each paper and for the pooled samples are presented. For
157 ongoing orthotic and therapeutic effects, data from studies reporting on the time frame ranging from 2-20 weeks were included for
158 analysis. There is currently no evidence to suggest when a therapeutic effect may occur following FES application, therefore a
159 pragmatic approach was taken that combined the minimum and median time frames reported in the papers selected for review.

160 **Results**

161 Literature search

162 The electronic literature search yielded a total of 125 articles, 8 from CINAHL, 67 from MEDLINE (OVID and EBSO), 29 from
163 Embase, 7 from Cochrane Library and 14 from PubMed databases. A hand search of reference lists yielded an additional 11
164 articles. Once duplicates were removed this yielded 90 articles for screening. The remaining 23 full text articles were reviewed (AS,
165 RH) and a further 3 were excluded. The remaining 20 articles, reporting on 19 studies involving 490 pwMS met the inclusion criteria
166 and were included in the quality review and meta-analysis. Results are presented in the PRISMA flowchart (Figure 2).

167 Study and participant characteristics

168 The characteristics of the studies and subjects are presented in Table 2. Eleven articles in the review used experimental designs,
169 including 1 randomized controlled trial (RCT)²⁵, 1 randomized crossover trial²⁶ and 8 non RCTs generating data in 9 articles²⁷⁻³⁵.
170 Nine articles presented data from 8 observational studies, including 1 case control³⁶ and 8 interrupted time series
171 designs^{12,13,37,38,40-42}. All studies recruited participants from hospitals or MS clinics and most recruited pwMS only^{13, 25-29, 31-40,42}.
172 Three studies recruited participants with different neurological diagnoses, where MS data could be extracted separately^{12,30,41}. The
173 20 articles recruited a total of 447 participants. Sample numbers in the majority of studies were generally small and ranged from 2⁴²
174 to 39¹³, however one retrospective observational study presented data from 153 participants⁴⁰. Most studies reported either a mix
175 of MS type or did not report MS type. Two studies recruited participants with secondary progressive MS only^{25, 26}. There were
176 similarities in the age, sex, time since diagnosis and disability level of the participants recruited across the studies. The mean age
177 of participants ranged from 46.5¹³ to 56³⁵ years and time since diagnoses ranged from 8.6³⁵ up to 17.7²⁵ years. Between 25 to 77 %
178 of participants recruited in the studies were female. Disability was only reported in 6 studies and ranged from Extended Disability
179 Status Score 3.5³² to 5.9²⁶. Walking aid use was frequently reported throughout the studies, indicating that participants had
180 significant walking impairment.

181 The detail given about inclusion and exclusion criteria varied. Some observational studies reported minimal detail^{12,31,37,41,42} other
182 than the inclusion of MS participants deemed suitable for FES while others^{12,25,28,30,37,41} did not indicate whether participants had
183 used FES prior to inclusion. Some studies recruited pwMS already using FES^{13,29,31,36,38,39,42} while others indicated previous FES

184 use as an exclusion^{26,27,34}. Some studies excluded potential participants unable to walk a minimum of 10 meters^{27, 29, 30}, whereas
185 others included only those able to walk longer distances, up to 6 minutes^{33,36,38,39,41}. Only 4 studies reported exclusion of potential
186 participants with unstable disease or recent relapse^{27,33,38,39}. Most studies gave no indication of exclusions related to medication.
187 Only 1 study excluded participants taking medication for fatigue or mobility³³; however another²⁷ actively recruited participants on a
188 stable dose of fampridine, a drug licensed for treating walking impairment in MS.

189 Interventions

190 Almost half of the studies investigated the single channel Odstock Dropped Foot Stimulator® (ODFS)^{a 25,28,29,31,32,35,36,39}. Four
191 articles included data from dual channel ODFS (for bilateral foot drop or foot drop plus gluteal stimulation) in addition to single
192 channel ODFS^{12,26,37,40}. Three studies evaluated the Walkaide® system^{b 27,30,34}, one study compared the ODFS with Walkaide®³⁸
193 and one study investigated the impact of the Ness L300® device^{c 33}. Two studies evaluated implantable FES, one study with the
194 STIMuSTEP^{a 13} and another with ActiGait®^{d 42}. The only RCT²⁵ compared single channel ODFS with an exercise programme. A
195 randomized crossover trial¹³ compared single channel ODFS followed by dual channel ODFS (anterior tibialis and guteal
196 stimulation) with weekly physiotherapy. A non-randomized controlled trial compared single channel ODFS with an AFO²⁹.

197 [Insert Table 2 here]

198 Outcome measures and effects

199 Details of the outcome measures used in each of the studies are presented in Table 3. All articles presented data on outcome
200 measures that assessed gait speed. Seventeen studies measured gait speed over short distances, with most tests indicating
201 participants walked at a fast pace. The majority of studies used the 10 metre Walk Test (10MWT)^{12,13,25,27,28-30,32,37,40,41,42} however 3
202 studies presented data on the 25 foot Walk Test (25ftWT)^{27,34,35} and two studies reported gait speed over a 6 metre walkway
203 (6MWT)^{31,33} as part of 3D gait analysis.

204 Walking speed over longer distances was less frequently reported. The range of walking tests used include: 6minWT^{27,28},
205 5minSSWS^{36,38,39}, 4minWT³⁰, 3minWT^{13,25} and 2minWT³². Data from the 6minWT and 3minWT are reported as the total distance
206 walked in the specified time, which was converted to walking speed for the purpose of analysis. All other tests are reported in m/s.
207 Some articles reported on other aspects of gait, which are described in Table 2, however any further analyses on these measures
208 are out of the scope of this review and will not be discussed further.

209 With regards to the short walking tests, all except 2 of the articles^{29,35} measuring this outcome reported on the initial orthotic effect
210 of FES. Nine studies reported a statistically significant increase in walking speed following initial application of FES, with effects
211 ranging from 5 to 18.3%^{12,26,28,30-32,34,40,41}. In contrast, 4 studies found no difference with FES^{25,27,33,37} and 2 small studies
212 investigating 2⁴² and 5²⁹ participants reported mixed results.

213 Thirteen articles reported on ongoing orthotic effects^{12,13,25,26,29,30,32,33,35,37,40-42} from 4 weeks^{29,35} up to a mean of 10.8 years¹² post
214 application. All of the studies except 2^{33,35} evaluating ongoing orthotic effects reported a statistically significant increase in walking
215 speed.

216 The therapeutic effect of FES on gait in short walking performance tests was reported in 11 articles^{12,13,25,26,30,32,33,37,40-42} at a
217 number of time points from 6 weeks²⁵ to a mean of 10.8 years¹² of FES application. One study reported a statistically significant
218 therapeutic effect at 12 weeks³⁰. The majority of articles found no therapeutic effect with small or no improvements in walking
219 speed^{25,26,32,33,37,40}. Four of the studies noted a reduction in unassisted walking speed at 12⁴² and 18 weeks⁴¹, and this was
220 significant in 2 studies at 3¹³ and a mean of 5.1 years¹².

221 Effects of FES on gait in long walking performance tests were reported less frequently. There were mixed results with reports of
222 initial positive orthotic effects in the 2minWT^{28,32}, 3minWT⁴¹ and 4minWT³¹ but not the 6minWT^{27,28}. Positive ongoing orthotic effects
223 were found from 6 weeks to 11 months^{13,25,30,32,42}. Two studies reported in 3 articles^{36,38,39} used the same protocol for the
224 5minSSWS and evaluated the impact of FES on established users of more than 6 months. Both studies noted significant ongoing
225 orthotic effects, except in participants already walking at baseline speeds of >0.8m/s³⁹.

226 The therapeutic effect of FES on longer walking tests was investigated in only 5 studies. There were mixed results with positive
227 effects being noted at 12 weeks^{30,32} and 11 months³⁰, but not at 12⁴² and 18 weeks^{13,25}.

228 [Insert Table 3 here]

229 Methodological quality

230 The methodological quality of the studies is detailed in Table 4. The global rating for methodological quality was moderate for 12
231 articles^{12,13,25,26,28,30, 32,34,35,37,40,41} while the remaining 8 articles received a global rating of weak^{27,29,31,33-36,42}. None of the 20 articles
232 gained an overall strong rating largely due to difficulty blinding participants and assessors with FES. All of the studies scored weak
233 on blinding thus indicating performance and detection bias. Twelve articles rated strong for data collection methods<sup>12,13,25,26,28-
234 30,32,34,36,37,40</sup>. One study rated strong for selection bias²⁵, one study rated weak²⁹ and all the others rated moderate. Study design
235 was rated moderate for all of the studies excluding 2 that were rated weak^{29,42}. For fifteen articles the confounders variable was not
236 applicable^{12,13,28-3,40,42} as there were no comparator control groups.

237 [Insert Table 4 here]

238 Analysis of overall effect

239 Eleven studies recruiting 353 participants were included in the meta-analysis for the initial orthotic effect of FES on gait speed for
240 short walking speed tests (Table 5). Eight articles with a total of 255 participants were included for meta-analysis of ongoing orthotic
241 effects (Table 5). Meta-analyses revealed evidence of a significant initial ($t = 2.14$, $p = 0.016$) and ongoing orthotic effect of up to 20
242 weeks ($t = 2.81$, $p = 0.003$) using FES for foot drop on gait speed in short walking performance tests in pwMS. Walking speed

243 increased by 0.05 meters per second (m/s) (7.1%) for the initial orthotic effect and 0.08m/s (11.3%) and for the ongoing orthotic
244 effect.

245 Six studies recruiting 244 participants were included in the meta-analysis for the therapeutic effect of FES on gait speed (Table 5).
246 Analyses of the pooled data found no change in gait speed in the short walking performance tests and thus no therapeutic effect
247 ($t=0.03$, $p=0.487$) with FES.

248 Five studies recruiting 89 participants were included in the meta-analysis for the initial orthotic effect on gait speed in long walking
249 performance tests (Table 6). Eighty one participants were included for analyses of the ongoing orthotic effect of FES. There was a
250 small non-significant increase in walking speed of 0.02m/s (3.3%) for the initial orthotic ($t=0.57$, $p=0.286$) and a small non-
251 significant increase of 0.04m/s (6.2%) for ongoing continued orthotic effect (of up to 20 weeks) ($t=0.94$, $p=0.174$) with FES (Table
252 6).

253 Only 3 studies recruiting 61 participants included data that was used to evaluate the therapeutic effect (up to 20 weeks) of FES on
254 gait speed in long walking performance tests. There was a 10.3% increase in walking speed noted, however this was non-
255 significant ($t=1.34$, $p=0.091$) (table 6).

256 *[Insert Tables 5 & 6 here]*

257 **Discussion**

258 This systematic review aimed to appraise the efficacy of FES for foot drop in pwMS on gait speed in short and long walking
259 performance tests. A systematic and inclusive approach was undertaken for study selection, with independent assessment of
260 quality and data extraction. In this review of 20 articles (19 studies) analysis of pooled data found a statistically significant initial
261 ($t=2.14$, $p=0.016$) and ongoing ($t=2.81$, $p=0.003$) orthotic effect of FES on gait speed in short walking performance tests, increasing
262 gait speed by 0.05 and 0.08m/s, respectively. No therapeutic effect was found. A change of 0.05m/s in walking speed is
263 considered to be clinically significant, with a change of 0.1m/s indicating a substantial clinical change⁴³. Therefore this review
264 identified effects of FES on walking that are meaningful to pwMS. FES produced small non-significant initial and ongoing orthotic
265 and therapeutic effects on gait speed in long walking performance tests.

266 Contradictory results however were found across the studies. The majority of studies reported statistically significant ongoing
267 orthotic effects for the short walk tests, however 2 studies did not. One of these studies recruited participants with lower disability
268 scores³³. Both studies recruited participants with baseline walking speeds of >0.8m/s (1.2m/s³³ and 0.83m/s³⁵). Miller et al.³⁹ had
269 previously found FES to have no orthotic effect in pwMS walking at gait speeds of >0.8m/s. These results therefore shed some
270 doubt on the use of FES in pwMS with lower levels of disability and faster baseline walking speeds. Further investigation of FES in
271 pwMS walking at faster gait speeds is required.

272 The majority of the studies evaluating therapeutic effects of FES on short walking tests reported no significant difference, however
273 3 studies reported a negative therapeutic effect^{13,26,42}. One of these studies recruited participants with secondary progressive MS,

274 where deterioration in walking speed is expected over time. The other 2 articles investigated implantable FES. Hausmann et al.⁴², a
275 study of only 2 participants, reported a negative therapeutic effect in 1 participant. Taylor et al.¹³ reported therapeutic effects over a
276 longer time frame (3 years) and although there was no detail given regarding MS type of recruited participants, the time since
277 diagnosis (mean of 17.3 years) is indicative of participants presenting with secondary progressive MS. The results from these
278 studies suggest that the potential therapeutic effect of FES may be limited in progressive MS patients, however further investigation
279 is warranted.

280 The National Institute for Health and Care Excellence (NICE) guidelines for FES for foot drop of central neurological origin⁴⁴ found
281 evidence to support the use of FES, however studies included in the NICE review were undertaken in stroke and not MS. There
282 has not been a systematic review specifically evaluating FES in MS although a recent narrative synthesis found positive orthotic,
283 but not therapeutic effects of FES on walking performance. This review recommended that FES be used to complement treatments
284 for walking limitation in MS and had potential to optimize functional outcomes¹⁴. The results from this systematic review supports
285 and further strengthens the recommendations of the NICE guidelines and the previous narrative review, by adding further evidence
286 in terms of the positive impact of FES in MS.

287 There have been 3 previous reviews of FES in stroke. A narrative synthesis¹⁴ reported positive orthotic effects of FES on gait
288 speed in chronic stroke, although there was less conclusive evidence of a therapeutic effect. Kottink et al.¹⁶ reviewed 8 studies and
289 reported an increase in gait speed of 0.13 m/s (0.07–0.2, 38%) with FES, that is larger than found in this review for short walk tests

290 (0.08m/s (-0.01-0.1, 11%)). Pereira et al.¹⁷ reviewed 7 RCTs and found a small but significant therapeutic effect with FES (0.379
291 m/s \pm 0.152; 95% CI, 0.081 to 0.677; $P = .013$) in the 6minWT in chronic stroke. This increase again is more than that found in the
292 current review for short walk tests (0m/s (-0.06-0.1, no change)); however it may be that potential therapeutic effects of FES may
293 be limited by the neurodegenerative nature of MS in comparison to a more acute condition such as stroke and this requires further
294 investigation.

295 Participants in the studies reviewed had mean Extended Disability Status Scores ranging from 3.5 (moderate disability in one
296 functional system and more than minimal disability in several others, no impairment to walking) to 6 (requires a walking aid (cane,
297 crutch, etc) to walk about 100 meters with or without resting). This sample is representative of pwMS with walking limitations for
298 whom we would expect a benefit from FES application. Participants in the lower Extended Disability Status Score range (3.5) who
299 have less obvious walking difficulties however may present with fatigable foot drop. Decreased ankle dorsiflexion at initial contact
300 has been found to worsen with fatigue⁴⁵ in pwMS. None of the studies in this review explicitly reported on recruitment of
301 participants presenting with fatigable foot drop. There is limited evidence that FES may not be beneficial for pwMS with less
302 disability, walking at faster speeds³⁹ however further investigation is warranted. .

303 The majority of the articles did not report on MS type which may limit the external validity of the findings of this review, however 2
304 studies specifically recruited people with secondary progressive MS^{12, 25}. The time since diagnosis was reported in all but 4 of the
305 articles and ranged between 9.79 to 17.7 years, which may be more indicative of secondary progressive MS.

306 Most studies reviewed give little detail around the inclusion and exclusion criteria used and where detail was given there was no
307 consistent approach taken. The use of medications and the effect of relapse and progression of disease may influence outcomes
308 and response to FES therefore the failure of most studies to report these variables may call the validity of results of the studies into
309 question.

310 There were only two randomized study designs in this review, indicating a high probability of selection bias and poor internal
311 validity. All studies scored weak for blinding signifying performance and detection bias to be significant factors. It is impossible to
312 blind physical treatments such as FES to participants and it is extremely difficult to blind assessors. There were no attempts to
313 separate FES application and outcome assessment in any of the studies, suggesting performance bias. The EPHP tool considers
314 both blinding and confounders in its scrutiny therefore both factors impact on the overall quality ratings.

315 Limitations

316 The primary limitation of this review was the low methodological quality of the studies included. The conclusions of this review must
317 therefore be treated with some caution until further high quality RCTs are undertaken. Although the EPHP quality assessment tool
318 has demonstrated acceptable levels of test re-test reliability and content and construct validity¹⁹, it was developed to evaluate
319 public health nursing and therefore may not have been the most appropriate tool for this review. Selection of this tool however was

320 based on the recommendations of previous systematic reviews^{19,20} and supports an inclusive approach which allowed the same
321 checklist and summary score to be used across all the studies.

322 This review was limited by the inclusion of English language papers and did not include unpublished studies or studies published in
323 grey literature which may limit its applicability. There remains a debate around publication bias and the usefulness of including
324 unpublished trials⁴⁶, however it is likely that any unpublished studies would be of poor quality and lack robust peer review ^{46,47}.

325 For the purpose of the meta-analyses data from a range of short and longer walking tests were combined. Although there is
326 evidence to support the comparability of the longer walking tests²³, there are also differences in the pace of the walking tests used
327 which may have influenced the results. A recent MS outcome measures taskforce document has also suggested that the 2minWT
328 should not be used in research due to the limited availability of psychometric data⁴⁸.

329 A pragmatic approach was taken which combined data across a range of assessment points (up to 20 weeks) in order to inform
330 continued orthotic and therapeutic effects. There is no evidence to suggest when optimal orthotic or therapeutic effects are likely to
331 occur and whether they remain stable over time. Using this approach therefore may have led to ambiguity with the results.

332 Fewer participants were included in the meta-analyses for the ongoing orthotic (n=81) and therapeutic (n=61) effects of FES on gait
333 speed on long walking performance tests, therefore there are limitations with regards to the strength of these findings. As no raw

334 data was available within group analysis was not viable and the between group analysis may not have detected subtle effects that
335 may have occurred.

336 FES is considered a device that should be used long term for orthotic purposes and in a progressive condition like MS this may
337 account for many years. Despite this, only one interventional study²⁶ reported on effects beyond 24 weeks, therefore the results of
338 this review are only applicable over the short to moderate term.

339 Implications for further research

340 Given the low methodology quality of the studies reviewed, future research should focus on adequately powered randomized trial
341 design with a control or comparator treatment arm, such as exercise or AFO. Improved consistency in reporting of methodology, as
342 recommended by the CONSORT guidelines⁴⁹ is also recommended. Consistent reporting of demographics including MS type,
343 disability level and baseline walking speed would allow for sub-group analysis. Future studies should include long term follow up
344 and investigate initial and ongoing orthotic and therapeutic effects of FES in order to understand its full potential as a treatment for
345 foot drop in MS.

346 This current review found a wide variation in the walking tests used between studies both in terms of distance, pace (fastest and
347 preferred) and methods of collection (mean of three, warm up then final test). Researchers should agree on the most valid, reliable
348 and clinically significant measures of gait speed using short and long walking performance tests to allow a more consistent

349 approach in future FES research. This review is limited to the impact of FES on gait speed in short and long walking performance
350 tests. Some of the articles reported measures of patient experience and quality of life and future studies should consider a mixed
351 methodological approach as recommended by the NICE guidelines ⁴⁴.

352 **Conclusion**

353 This review found evidence of initial and ongoing orthotic effects of FES for foot drop in MS on gait speed in short walking tests
354 which were clinically meaningful, but did not find evidence of orthotic or therapeutic effects of FES on long walking tests. However
355 due to the poor methodological quality of studies undertaken to date, caution must be applied in making recommendations to
356 clinical practice. There is limited evidence of the comparative effectiveness of FES with other treatments. Future research should
357 focus on adequately powered randomized trial design with a control or comparator treatment arm, using valid and reliable
358 measures of gait speed that can detect clinically meaningful effects.

359

360 **Suppliers**

- 361 a. Odstock Medical Limited, Salisbury, UK
- 362 b. Innovative Neurotronics Inc., Austin, TX, USA
- 363 c. Bioness Inc., Valencia, CA, USA

364 d. Otto Bock Health Care, Duderstadt, Germany

365

366 **References**

367 1. Compston A, Coles A. Multiple sclerosis. Lancet 2008;372:1502-1517.

368 2. Noseworthy JH, Lucchinetti C, Rodriguez M, et al. Multiple sclerosis. N Engl J Med 2000;343:938-952.

369 3. Murray TJ. Diagnosis and treatment of multiple sclerosis. BMJ 2006; Mar (Clin Res ed) 332(7540):525-7.

370 4. Mackenzie IS, Morant SV, Bloomfield GA, et al. Incidence and prevalence of multiple sclerosis in the UK 1990-2010:a descriptive
371 study in the general practice research database. J Neurol Neurosurg Psychiatry 2014;85:76-84.

372 5. Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. Brain 2006;129:606-616.

373 6. Hobart J, Blight A, Goodman A, et al. Timed 25-foot walk: direct evidence that improving 20% or greater is clinically meaningful
374 in MS. Neurology 2013;80:1509-17.

375 7. Nilsagard Y, Lundholm C, Gunnarsson LG, et al. Clinical relevance using timed walk tests and 'timed up and go' testing in
376 persons with multiple sclerosis. Physiother Res Int 2007;12:105–114.

- 377 8. Gijbels D, Alders G, Van Hoof E, et al. Predicting habitual walking performance in multiple sclerosis: relevance of capacity and
378 self-report measures. *Mult Scler* 2010;16:618–626.
- 379 9. Gijbels D, Dalgas U, Romberg A et al. Which walking capacity tests to use in multiple sclerosis? A multicentre study providing
380 the basis for a core set. *MSJ* 2012;18(3):364–371.
- 381 10. Gunn H, Creanor S, Haas B, et al. Frequency, characteristics and consequences of falls in multiple sclerosis: findings from a
382 cohort study. *Arch Phys Med Rehabil* 2014; 95(3): 538-545.
- 383 11. Liberson WT, Holmquest HJ, Scot D, et al. Functional electrotherapy: stimulation of the peroneal nerve synchronized with the
384 swing phase of the gait of hemiplegic patients. *Arch Phys Med Rehabil* 1961; 42: 101–5.
- 385 12. Taylor P, Humphries L, Swain I. The long-term cost-effectiveness of the use of functional electrical stimulation for the correction
386 of dropped foot due to upper motor neuron lesion. *J Rehabil Med* 2013;45(2):154-160.
- 387 13. Taylor PN, Wilkinson-Hart IA, Khan MS, et al. The correction of dropped foot due to multiple sclerosis using the STIMuSTEP
388 implanted dropped foot stimulator. *Int J MS Care* In-Press [serial online] 2016. Available from: [http://dx.doi.org/10.7224/1537-](http://dx.doi.org/10.7224/1537-2073.2015-038)
389 2073.2015-038
- 390 14. Dapul G, Bethoux F. Functional electrical stimulation for foot drop in multiple sclerosis. *US Neurology* 2015:10-18.

- 391 15. Roche A, Laighin GO, Coote S. Surface-applied functional electrical stimulation for orthotic and therapeutic treatment of drop
392 foot after stroke: a systematic review. *Phys Ther Rev* 2009;14(2):63-80.
- 393 16. Kottink AIR, Oostendorp LJM, Buurke JH et al. The orthotic effect of functional electrical stimulation on the improvements of
394 walking in stroke patients with a dropped foot: a systematic review. *Artif Organs* 2004;28(6):577-86.
- 395 17. Pereira S, Mehta S, McIntyre A, et al. Functional electrical stimulation for improving gait in persons with chronic stroke. *Top*
396 *Stroke Rehabil* 2012;19(6):491-8.
- 397 18. Katrak P, Bialocerkowski A, Massy-Westropp, et al. A Systematic review of the content of critical appraisal tools. *BMC Medical*
398 *Research Methodol* 2004 Sep 16;4: 22.
- 399 19. Thomas BH, Ciliska M, Dobbins M, et al. A process for systematically reviewing the literature: providing the research evidence.
400 *Worldviews Evid.-Based Nurs* 2004;1:176-184.
- 401 20. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. *Health Technol. Assess* 2003;7:iii- x,
402 173.
- 403 21. Sanderson S, Tatt DI, Higgins JPT. Tools for assessing quality and susceptibility to bias in observational studies in
404 epidemiology: a systematic review and annotated bibliography. *Int J. Epidemiol* 2007;36:666-676.

- 405 22. Everitt, B.S. Cambridge of statistics in the medical sciences. Cambridge UK: Cambridge University Press 1995.
- 406 23. Gijbels D, Eijnde BO, Feys P. Comparison of the 2- and 6-minute walk test in multiple sclerosis. Mult Scler 2011;17(10):1269-
407 72.
- 408 24. Tomlinson A, Khanal S, Ramaesh K, et al. Tear Film Osmolarity: Determination of a referent for dry eye diagnosis. Invest
409 Ophthalmol. Vis Sci 2006;47(10).
- 410 25. Barrett CL, Mann GE, Taylor PN, et al. A randomized trial to investigate the effects of functional electrical stimulation and
411 therapeutic exercise on walking performance for people with multiple sclerosis. Mult Scler 2009;15:493-504.
- 412 26. Taylor P, Barrett C, Mann G, et al. A feasibility study to investigate the effect of functional electrical stimulation and
413 physiotherapy exercise on the quality of gait of people with multiple sclerosis. Neuromodulation 2014;17:75-84.
- 414 27. Mayer L, Warring T, Agrella S, et al. Effects of electrical stimulation on gait function and quality of life for people with multiple
415 sclerosis taking dalfampridine. Int J MS Care 2015;17:35-41.
- 416 28. Scott SM, Van der Linden ML, Hooper JE, et al. Quantification of gait kinematics and walking ability of people with multiple
417 sclerosis who are new users of functional electrical stimulation. J Rehabil Med 2013;45:364-69.

- 418 29. Sheffler LR, Norgan Bailey S, Chae J. Spatiotemporal and kinematic effect of peroneal nerve stimulation versus an ankle- foot
419 orthosis: A case series. *Am J Phys Med Rehabil* 2009a;1:604-11.
- 420 30. Stein R, Everaert DG, Thompson AK, et al. Long term therapeutic and orthotic effect of a foot drop stimulator on walking
421 performance in progressive and non-progressive neurological disorders. *Neurorehabil Neural Repair* 2010; 24:152-167.
- 422 31. Van der Linden M, Scott S, Hooper J, et al. Gait kinematics of people with multiple sclerosis and the acute application of
423 functional electrical stimulation. *Gait Posture* 2014a; 39: 1092–1096.
- 424 32. Van der Linden M, Hooper J, Cowan P, et al. Habitual functional electrical stimulation therapy improves gait kinematics and
425 walking performance, but not patient-reported functional outcomes, of people with multiple sclerosis who present with foot-drop.
426 *PLOS ONE* 2014(b); 9: 1-9.
- 427 33. Barr C, Patriitti B, Bowes R, et al. Orthotic and therapeutic effect of functional electrical stimulation on fatigue induced gait
428 patterns in people with multiple sclerosis. *Disabil Rehabil Assist Technol* 2016;12(52):1-1331.
- 429 34. Downing A, Van Ryn D, Fecko A, et al. Effect of a 2 week trial of functional electrical stimulation on gait function and quality of
430 life in people with multiple sclerosis. *Int J MS Care* 2014;16(3):146-152.

- 431 35. Sheffler L, Hennessey M, Knutson J, et al. Neuroprosthetic Effect of peroneal nerve stimulation in multiple sclerosis: a
432 Preliminary Study. Arch Phys Med Rehabil 2009b;90:362-365.
- 433 36. Paul L, Rafferty D, Young S, et al. The effect of functional electrical stimulation on the physiological cost of gait in people with
434 multiple sclerosis. Mult Scler 2008;14:954-61.
- 435 37. Barrett C, Taylor P. The effects of the Odstock drop foot stimulator on perceived quality of life for people with stroke and
436 multiple sclerosis. Neuromodulation 2010;13:58-64.
- 437 38. Miller L, Rafferty D, Paul L et al. A comparison of the orthotic effect of the Odstock dropped foot stimulator and the Walkaide
438 functional electrical stimulation systems on energy cost and speed of walking in multiple sclerosis. Disabil Rehabil Assist Technol,
439 2015;10(6):482-85.
- 440 39. Miller L, Rafferty D, Paul L et al. The impact of walking speed on the effects of functional electrical stimulation for foot drop in
441 people with multiple sclerosis. Disabil Rehabil Assist Technol 2016;11(6):478-83.
- 442 40. Street T, Taylor P, Swain I. The effectiveness of functional electrical stimulation on walking speed, functional walking category
443 and clinically meaningful changes for people with multiple sclerosis. Arch Phys Med Rehabil 2015;96(4):667-672.

- 444 41. Taylor P, Burridge J, Dunkerly A, et al. Clinical use of the Odstock dropped foot stimulator: it's effect on the speed and effort of
445 walking. Arch Phys Med Rehabil 1999;80:1577-1583.
- 446 42. Hausmann J, Sweeney-Reed C, Sobieray U, et al. Functional electrical stimulation through direct 4-channel nerve stimulation to
447 improve gait in multiple sclerosis: a feasibility study. J Neuroeng Rehabil 2015;12(100):1-9.
- 448 43. Pereira S, Mody SH, Woodman RC, et al. Meaningful change and responsiveness in common physical performance measures
449 in older adults: meaningful change and performance. J Am Geriatr Soc 2006;54:743-749.
- 450 44. National Institute for Health and Care Excellence (NICE). Functional electrical stimulation for foot drop of central neurological
451 origin; interventional procedure guidance. United Kingdom [IPG278] 2009. .
- 452 45. McLoughlin JV, Barr CJ, Patrilli B et al. Fatigue induced changes to kinematic and kinetic gait parameters following six minutes
453 of walking in people with multiple sclerosis. Disabil Rehabil. 2016;38:535-543.
- 454 46. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. West Sussex: John Wiley & Sons Ltd; 2008.
- 455 47. Egger M, Ju'ni P, Bartlett C, et al. How important are comprehensive literature searches and the assessment of trial quality in
456 systematic reviews? Empirical study. Health Technology Assessment 2003;7:1.

457 48. Potter K, Allen D, Bennett S, et al. Multiple sclerosis outcome measures taskforce [serial online]. Available from: URL:

458 <http://www.neuropt.org/docs/ms-edge-documents/final-ms-edge-document.pdf?sfvrsn=4>

459 49. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials.

460 *Ann Intern Med* 2010;152:726–732.

461

462 **Figure and table legends**

463 **Table1: Search strategy for databases**

Database	Search Strategy
CINAHL via EBSCO	((MS OR "multiple sclerosis") AND (Drop foot OR foot drop) AND ((Gait OR walk*) AND ((FES OR "functional electrical stimulation" OR electric* OR stimulat* OR "neuromuscular electrical stimulation" OR EMS OR peroneal nerve stimulat*)))
Cochrane Library	("Multiple Sclerosis" or MS:ti,ab,kw and functional electrical stimulation or FES or "neuromuscular electrical stimulation" or "EMS" or electric or stimulat:ti,ab,kw or peroneal nerve stimulation and Drop foot or foot Drop:ti,ab,kw and gait or walk:ti,ab,kw (Word variations have been searched))
Embase via Ovid	((MS OR "multiple sclerosis").mp.) AND ((Drop* AND foot).mp.) AND ((Gait OR walk*).mp.) AND ((FES OR "functional electrical stimulation" OR electric* OR stimulat* OR "neuromuscular electrical stimulation" OR EMS OR peroneal nerve stimulat*).mp.))
MEDLINE via Ovid	((MS OR "multiple sclerosis").mp.) AND ((Drop* AND foot).mp.) AND ((Gait OR walk*).mp.) AND ((FES OR "functional electrical stimulation" OR electric* OR stimulat* OR "neuromuscular electrical stimulation" OR EMS OR peroneal nerve stimulat*).mp.))
MEDLINE via EBSCO	((MS OR "multiple sclerosis") AND (Drop foot OR foot drop) AND ((Gait OR walk*) AND ((FES OR "functional electrical stimulation" OR electric* OR stimulat* OR "neuromuscular electrical stimulation" OR EMS OR peroneal nerve stimulat*)))
PubMed	Multiple sclerosis AND foot drop AND gait AND functional electrical stimulation

464

465 **Table 2: Summary of study design, sample information, outcome measures, assessment points and potential sources of**
 466 **bias of selected studies.** (key: N=numbers of participants, NR=not reported, pwMS=people with MS, SPMS=secondary
 467 progressive MS, PP=primary progressive, RR=relapsing remitting, DF=dorsiflexion, PF=plantarflexion, EDSS=Extended Disability

468 Status Scale, HAI=Hauser Ambulation index, L/L=lower limb, HSP=Hereditary Spastic Paraplegia, FAP=Functional Ambulation
 469 Profile, MSWS-12=Multiple Sclerosis Walking Scale-12, MSIS-29=Multiple Sclerosis Impact Scale-29, PIADS=Psychological
 470 Impact of Assistive Device Scale,SF-36= short form-36, FWC=Functional Walking Category, PCI=Physiological Cost Index,
 471 ROGA=Rivermead Observational Gait Analysis, s=seconds, m=meters, ft=feet, wks=weeks, min=minute, mths=months,
 472 meds=medications)

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
Barr et al. ²⁵ Experimental: non-RCT	11 NR 47 7:4 NR 3.5	Inclusions •EDSS score 3-6 •Unilateral foot drop •Able to walk for 6min Exclusions •Relapse <3mo	T=Ness L300 NR	0, 8	6MWT None Gait analysis ^f	•Small sample •Narrow EDSS range •? effect of fast baseline walking speeds •Assessors not blinded

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
		<ul style="list-style-type: none"> •Fatigue or mobility medications •Contraindications to FES •Regularly uses AFO •Unable to achieve passive DF to plantigrade 				
Barrett et al ²⁶ Experimental: RCT (FES vs exercise)	20 (T: n=20; C: n=24) SPMS T: 52.1 \pm 6.7; C: 56.6 \pm 9 T: 15/5; C: 16/8 T: 13.6 (8.3); C: 17.7 (8.3) T: 5.9 (0.8); C: 5.8 (0.8)	Inclusions <ul style="list-style-type: none"> •>18y •SPMS •EDSS score 4–6.5 •Unilateral foot drop •Passive DF to plantigrade 	T=ODFS, C=home exercises T=unrestricted daily use after 2wk, C=exercises performed daily (30min)	0, 6, 12, 18	10MWT 3minWT PCI (10m)	<ul style="list-style-type: none"> •High dropout rate •No baseline assessment without FES •Assessors not blinded •Assessors providing treatment (measurement bias) •Underpowered

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
		<ul style="list-style-type: none"> •Good response to FES Exclusions <ul style="list-style-type: none"> •Other neuro/ortho problem affecting gait •Cognitive/psychiatric problem affecting compliance 				<ul style="list-style-type: none"> •Potential for fatigue during longer walking tests
Barrett and Taylor ²⁷ Observational: interrupted time series	20 NR 56 \pm 6.9 12:8 10.7 (7.7) NR	•pwMS attending FES clinic from January 2005–January 2006	T=ODFS (n=16), dual channel (n=4) Unrestricted use	0, 18	10MWT None PIADS	<ul style="list-style-type: none"> •Clinical audit data •Small sample •Assessors not blinded •Potential bias from questionnaires being administered by clinical staff providing treatment

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
Downing et al ²⁸ Experimental: non-RCT	19 RR: n=10; SP: n=5; PP: n=4 51.8 \pm 10.2 10:9 9 (7,9) NR	Inclusions •Able to walk 25ft >8s and <45s •Not currently using FES Exclusions •Relapse <60d •Requires AFO for stance •Epilepsy •Previous botulinum toxin in L/L last 6mo •Baclofen pump last 3mo •Peripheral nerve injury	T=WA Gradual build up to full-time wear over 2wk	0, 2	25ftWT None MSWS12, MSIS29	•Small convenience sample •No blinding or comparator •Limited follow-up period
Hausmann et al ²⁹ Observational:	2 SP: n=1; PP: n=1	Inclusions	ActiGait	0, 12	10MWT 3minWT	•Feasibility study: case report of 2 participants

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
interrupted time series	49.5 1:1 10.5 5	<ul style="list-style-type: none"> •Previous surface FES, benefits noted but sensory side effect not tolerated/difficulty positioning electrodes 			Gait analysis, ^f SF-36	
Mayer et al ³⁰ Experimental: non-RCT	20 RR: n=8; SP: n=8; PP: n=4 51.7 12:8 15.8 NR	<p>Inclusions</p> <ul style="list-style-type: none"> •Stable dose of fampridine for 12wk •Leg weakness, slow gait, and foot drop ($<-5^\circ$ PF during swing) •Able to walk 25ft $>8s$ and $<45s$ •Not currently using FES <p>Exclusions</p> <ul style="list-style-type: none"> •Relapse $<60d$ 	T=WA Daily walking	-2, 0, 4, 12	25ftWT 6minWT GAITRite ^l , FAP, MSWS12, SF-36	<ul style="list-style-type: none"> •Small sample •Convenience sample •Possible concurrent or enhanced effect of fampridine

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
		<ul style="list-style-type: none"> •Requires AFO for stance •Epilepsy •Previous botulinum toxin in L/L last 6mo •Baclofen pump last 3mo •Peripheral nerve injury 				
Miller et al ³¹ Observational: interrupted time series	20 RR: n=9; SP: n=9; PP: n=2 50.4 \pm 7.3 10:10 11.2 (8.6) EDSS NR but HAI between 2 and 7	Inclusions <ul style="list-style-type: none"> •Established FES user (>6mo) •Can walk for 5min •HAI 2–6 Exclusions <ul style="list-style-type: none"> •Recent relapse (6wk) 	T=ODFS compared with walkaide ^c One off application only	0 (variable length of using FES [mean, 2 y; SD, 5.75])	None 5minSSWS Energy cost of walking ^a	<ul style="list-style-type: none"> •Small sample •Single variable assessment time point •Recruitment of established FES users •pwMS had limited time to adapt to walkaide^c application •Assessors not blinded

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
		•Other neuro/ortho condition affecting gait				
Miller et al ³² Observational: interrupted time series Post hoc analysis of Miller et al (analysis of 2 groups based on walking speed)	20 (group 1 [n=11]: <0.8m/s; group 2 [n=9]: >0.8m/s) RR: n=9; SP: n=9; PP: n=2 50.4 \pm 7.3 10:10 11.2 (8.6) 5.3 (2)	Inclusions •Established FES user (>6mo) •Can walk for 5 min •HAI 2–6 Exclusions •Recent relapse (6wk) •Other neuro/ortho condition affecting gait	T=ODFS One off application only	0 (variable length of using FES [mean, 2 y; SD, 5.75])	None 5mSSWS Energy cost of walking ^a	•Small sample •Single variable assessment time point •Recruitment of established FES users •Assessors not blinded
Paul et al ³³ Observational: case-control	24 (T: n=12; C: n=12 [healthy matched controls]) RR: n=2; SP: n=10 P	Inclusions •18–65y	T=ODFS One off application only	0 (variable length of FES use 7mo–7y)	None 5minSSWS Energy cost of walking ^a	•Small sample •Single variable time point

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
	53 \pm 8 NR 9.8 NR	<ul style="list-style-type: none"> •Establish FES user (>6mo) Exclusions <ul style="list-style-type: none"> •Other neuro/ortho condition affecting gait 				<ul style="list-style-type: none"> •Recruitment of established FES users •Assessors not blinded
Scott et al ³⁴ Experimental: non-RCT	12 NR 47.8 \pm 6.6 3:9 NR NR	Inclusions <ul style="list-style-type: none"> •18–70y •Observable foot drop, suitable for FES Exclusions <ul style="list-style-type: none"> •Pregnant or breast feeding (patients experiencing a relapse were withdrawn) 	T=ODFS Initially 4x visits separated by >3 but <14d, then habitual use	0 (0–14d: mean of 4 walks within initial 14d)	10MWT 6minWT Gait analysis ^f	<ul style="list-style-type: none"> •Small sample •Large SDs of results •Acute application only •Possibility of effect of fatigue on walking tests

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
Sheffler et al ³⁵ Experimental: non-RCT	5 NR 50 3:1 11.8 NR	<p>Inclusions</p> <ul style="list-style-type: none"> •Diagnosed >6mo •DF strength <4 on MRC •Previously used AFO •Able to walk 30ft •Used FES for minimum of 4wk <p>Exclusions</p> <ul style="list-style-type: none"> •No sensation on L/L •PF contracture •Ataxia •Other neuro condition •Severe cognitive impairment 	T=ODFS One off application only	4	10MWT NR Gait analysis ^f	

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
		•Medical/neuro instability				
Sheffler et al ³⁶ Experimental: non-RCT	11 NR 52.1 \pm 12 8:3 8.6 (4.4) NR	Inclusions •Diagnosed >6mo •Previously used AFO >3mo •Used FES for minimum 4wk Exclusions •No sensation on L/L •PF contracture •Other neuro condition •Severe cognitive impairment •Medical/neuro instability	T=ODFS Maximum 8h/d for 4wk	4	25ftWT NR mEFAP	•Small convenience sample •No blinding or comparator •Only 50% of those screened found eligible •? sensitivity of OMs

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
Stein et al ²⁷ Experimental: non-RCT	31 (results reported for 22, which includes 1 HSP) NR (diagnosed >6mo) 54.2 \pm 9.9 15:16 11.5 (8.7) NR	Inclusions <ul style="list-style-type: none"> •Foot drop •>6mo diagnosed •Adequate cognitive and communication function •Able to walk 10m Exclusions <ul style="list-style-type: none"> •Poor response to FES •>1 fall per week •Severe cardiac disease/pacemaker •PF contracture >5° •Walking speed >1.2m/s •Unable to operate FES 	T=WA Unlimited daily use	0, 4, 8, 12, 48 Reported at 0, 12, 48wk	10MWT 4minWT PCI (10m)	

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
		•Terminal illness				
Street et al ³⁸ Observational: interrupted time series	187 (153 analyzed at 20wk) NR 55 117:70 11.7 NR (EDSS>7)	Inclusions •Referred sample issued FES (2008–2013) Exclusions •Unable to walk 10m •Poorly controlled epilepsy •Fixed skeletal deformity •Cardiac pacemaker	T=ODFS (n=178) dual channel (n=9) NR	0, median 20 (interquartile range, 16–24)	10MWT NR Clinically meaningful change in walking speed, change in FWC, reasons for not using	
Taylor et al ⁴² Observational: interrupted time series	23 NR 55.8 \pm 9.1 NR 14.6 (12.5)	Inclusions •Unilateral foot drop •Response to FES	T=ODFS NR	0, 18	10MWT NR PCI (10m)	•Small sample •Clinical audit data •Altered PCI protocol ? validity

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
	NR (walks a min of 10m)	<ul style="list-style-type: none"> •Able to walk 10m and sit-stand unaided •Tolerates sensation •Understands FES use 				
Taylor et al ¹² Observational: interrupted time series	39 NR 50.4 \pm 9.1 25:13 13.5 (8.4) NR (mean walking distance able 100m)	Inclusions <ul style="list-style-type: none"> •Referred sample (pwMS who received FES in 1999) 	T=ODFS or dual-channel stimulator NR	0, \geq 14 up to 10.8y	10MWT NR Clinically meaningful change in walking speed	<ul style="list-style-type: none"> •Retrospective clinical audit •No blinding/comparator or randomization
Taylor et al ³⁹ Experimental: individual RCT (crossover)	26 (group 1: n=12; group 2: n=14) SPMS: n=26 Group 1: 54.6 \pm 9.4;	Inclusions <ul style="list-style-type: none"> •SPMS •EDSS score <6.5 •Unilateral foot drop 	T=ODFS and dual-channel ODFS (DF and glutes) Daily use	-4, 0, 6, 12, 18, 24	10MWT NR ROGA, MSIS29, fall frequency	<ul style="list-style-type: none"> •Small sample •? comparability of the 2 groups

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
	group 2: 56.9 \pm 7.8 Group 1: 8:4; group 2: 10:4 Group 1: 12.2 (8.6); group 2: 14.5 (7.5) Group 1: 5.4; group 2: 5.9	<ul style="list-style-type: none"> •Gluteal weakness <4 (MRC) and instability of trunk, pelvis, or hip •Not used FES previously •Effective response to FES Exclusions <ul style="list-style-type: none"> •Reduced cognition affecting compliance •Coexisting medical condition affecting gait •Unable to walk without FES/AFO 				<ul style="list-style-type: none"> •Feasibility study/not fully powered •Assessor not blinded
Taylor et al ¹³ Observational:	23 (20 included in analysis) NR 56.5 \pm 11.3	Inclusions <ul style="list-style-type: none"> •Referred for STMuSTEP between 2006 and 2013 	T=STIMuSTEP ^b	0 (mean, 128d)	10MWT 3minWT	•Retrospective clinical audit

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
interrupted time series	NR 17.3 (11.5) NR	<ul style="list-style-type: none"> •Able to walk minimum 10m •External FES used for minimum of 6mo Exclusions <ul style="list-style-type: none"> •Contraindications for external FES •Diabetes, GA risk, currently on immunosuppressant drugs 			PCI, SF-36, PIADS	<ul style="list-style-type: none"> •Selection of participants – lack of generalizability of results •Missing data •No blinding/comparator or randomization •No comparison with predevice walking •No distinct follow-up period for direct comparison
Van der Linden et al ⁴⁰ Experimental: non-RCT Some of the participants were recruited from	22 (T [pwMS]: n=22; C [age matched healthy controls]: n=11) NR 49.4 \pm 7	Inclusions <ul style="list-style-type: none"> •Using FES for<3wk 	T=ODFS One off application only	0	6MWT NR Gait analysis ^f	<ul style="list-style-type: none"> •Small sample •Underpowered •Matched controls did not walk at range of speeds of pwMS

Reference and Design	Sample Information: No. of pwMS (T, treatment group; C, control) MS Type Age (mean \pm SD, where available) (y) Sex (F:M) Time Since Diagnosis (y) EDSS	Sample Information	Intervention Frequency of Use	Assessment Points Reported (wk)	Outcome Measures: Short Walk Test Long Walk Test Other	Limitations/Potential Sources of Bias/Other Comments
Scott et al ³⁴ (ie, 12 of the total 22)	11:11 NR NR					<ul style="list-style-type: none"> •? affect of walking aids in treatment group •Unblinded assessors
Van der Linden et al ⁴¹ Experimental: non-RCT	9 NR 53 \pm 9 7:2 NR NR	<p>Inclusions</p> <ul style="list-style-type: none"> •18–75y •Observable foot drop •Passive DF to plantigrade at ankle <p>Exclusions</p> <ul style="list-style-type: none"> •Weakness in lower limb (unable to bend/hold leg in supine) •Not walking in the community •Fixed L/L deformity 	T=ODFS NR	-4, 0, 6, 12	10MWT 2minWT RPE, Gait analysis, ^f daily step count, ^h MSIS29, FSS, MSWS12	<ul style="list-style-type: none"> •Small sample •Underpowered pilot study •No control group •Assessor not blinded

474 **Table 3: Summary of outcome measures used, effects measured (initial, ongoing and therapeutic) and results for gait**
475 **speed in short walking performance tests (10 meter walk test (10MWT), 25 foot walk test (25ftWT), 6 meter walk test**
476 **(6MWT)) and long walking performance tests (6 minute walk test (6minWT), 5 minute self-selected walking speed**
477 **(5minSSWS), 4 minute walk test (4minWT), 3 minute walk test (3minWT) and 2 minute walk test (2minWT)). (Key: ↑ increase,**
478 **↓decrease, sig=statistically significant, °=not statistically significant, NR=not reported, m=meters, s=seconds, m/s=meters per**
479 **second, wks=weeks, mths=months).**

Article	Short Walking Performance Tests Test Used Pace/Measured in Other Details	Orthotic Effect		Therapeutic Effect	Long Walking Performance Tests Test Used Measured in Other Details	Orthotic Effect		Therapeutic Effect (8–20wk)
		Initial	Ongoing (up to 20wk)			Initial	Ongoing (up to 20wk)	
Barr et al ²⁵	6MWT SSWS, m/s Mean of 3 trials	*Sig diff with FES	*Sig diff with FES	*Sig diff with FES	NR	NR	NR	NR
Barrett et al ²⁶	10MWT SSWS (m/s)	*Sig diff with FES	Sig ↑ with FES at 6, 12, 18wk (P=.001)	*Sig diff with FES at 18wk	3minWT Distance walked, m	NR	Sig ↑ with FES at 6 (P=.01), 12 (P=.003), and 18wk (P=.004)	*Sig diff with FES
Barrett and Taylor ²⁷	10MWT Pace NR, m/s	*Sig diff with FES	Sig ↑ with FES at 18wk (P=.001)	*Sig diff with FES	NR	NR	NR	NR
Downing et al ²⁸	25ftWT Fastest safe	Sig ↑ with FES	NR	NR	NR	NR	NR	NR

Article	Short Walking Performance Tests Test Used Pace/Measured in Other Details	Orthotic Effect		Therapeutic Effect	Long Walking Performance Tests Test Used Measured in Other Details	Orthotic Effect		Therapeutic Effect (8–20wk)
		Initial	Ongoing (up to 20wk)			Initial	Ongoing (up to 20wk)	
	speed/s Mean of 2 trials	($P=.0004$, 18.3%)						
Hausmann et al ²⁹	10MWT Pace NR, m/s	Patient 1: *Sig diff with FES Patient 2: Sig ↑ with FES ($P=.006$)	Patient 1: *Sig diff with FES Patient 2: Sig ↑ with FES ($P=.006$) at 12wk	Patient 1: ↓ walking speed without FES at 12wk	Max distance walked, m	Patient 1: Sig ↑ with FES ($P=.022$) Patient 2: Sig ↑ with FES ($P=.04$)	Increase in walking distance with FES compared with without FES at 12wk	Therapeutic effect noted in both patients
Mayer et al ³⁰	25ftWT Pace NR, ft/s Screening without FES=baseline without FES	*Sig diff with FES	NR	NR	6minWT Distance walked, m	*Sig diff with FES (↑ 10%)	NR	NR
Miller et al ³¹	NR	NR	NR	NR	5minSSWS SSWS, m/s	NR	Sig ↑ with ODFS ($P=.043$) Non sig ↑ with walkaide ^c ($P=.06$)	NR
Miller et al ³²	NR	NR	NR	NR	5minSSWS SSWS, m/s	NR	Sig ↑ with FES ($P=.043$) Sig ↑ with slow walkers (<0.8m/s) ($P=.005$) *Sig effect with	NR

Article	Short Walking Performance Tests Test Used Pace/Measured in Other Details	Orthotic Effect		Therapeutic Effect	Long Walking Performance Tests Test Used Measured in Other Details	Orthotic Effect		Therapeutic Effect (8–20wk)
		Initial	Ongoing (up to 20wk)			Initial	Ongoing (up to 20wk)	
							fast walkers (>0.8m/s)	
Paul et al ³³	NR	NR	NR	NR	5minSSWS SSWS, m/s	NR	Sig ↑ with FES ($P=.004$; 15.1%)	NR
Scott et al ³⁴	10MWT Time to walk, s	Sig ↑ with FES ($P=.004$)	NR	NR	6minWT Distance walked, m	*Sig diff with FES	NR	NR
Sheffler et al ³⁵	10MWT SSWS, m/s	NR	Variable response. 1 out of 5 noted sig ↑ with FES at 4wk	NR	NR	NR	NR	NR
Sheffler et al ³⁶	25ftWT Pace NR, s	NR	*Sig diff with FES at 4wk	NR	NR	NR	NR	NR
Stein et al ³⁷	10MWT Maximal safe speed, m/s	Sig ↑ with FES ($P<.001$; 3.9%)	Sig ↑ with FES ($P<.001$; 6.7%) at 12wk Non Sig ↑ at 11mo (4.1%)	Sig ↑ with FES ($P<.001$; 5.3%) at 12wk Non Sig effect at 11mo (5.6%)	4minWT, m/s Max safe walking speed	Sig ↑ with FES ($P<.001$; 2.3%)	Sig ↑ with FES ($P<.001$; 5.7%) at 12wk and 11mo (4.8%)	NR
Street et al ³⁸	10MWT Pace NR, m/s 3 walks, fixed	Sig ↑ with FES ($P<.001$; 14%)	Sig ↑ with FES at 20wk	*Sig diff with FES	NR	NR	NR	NR

Article	Short Walking Performance Tests Test Used Pace/Measured in Other Details	Orthotic Effect		Therapeutic Effect	Long Walking Performance Tests Test Used Measured in Other Details	Orthotic Effect		Therapeutic Effect (8–20wk)
		Initial	Ongoing (up to 20wk)			Initial	Ongoing (up to 20wk)	
	order: warm-up, without/with		($P<.001$; 27%)					
Taylor et al ⁴²	10MWT Brisk pace, m/s Mean of 3 with/3 without randomized order	Sig ↑ with FES ($P<0.01$; 5%)	Sig ↑ 10MWT ($P<.05$; 16%) with FES at 18wk	Non sig ↓ at 18wk (7%)	NR	NR	NR	NR
Taylor et al ³⁹	10MWT Pace NR, m/s No. of walks NR	Sig ↑ with FES ($P<.0001$; 16.2%)	Sig ↑ with FES at ≥ 14 wk ($P<.0001$; 15.4%)	Sig ↓ at ≥ 14 wk ($P<.08$)	NR	NR	NR	NR
Taylor et al ¹³	10MWT Briskly but safely, 2 walks without followed by 2 walks with FES, m/s	NR	Sig ↑ with FES at 18wk ($P<.001$) and 3y ($P<.004$)	*Sig effect with FES at 38wk; however 3 did achieve ↑ of 16.67% Sig ↓ unassisted walking speed at 3y ($P=.14$)	3minWT Walking along a 14-m corridor, pace NR, m	NR	Sig ↑ with FES at 18wk ($P<.001$)	↓ in unassisted walking speed at 18wk
Taylor et al ¹²	10MWT Pace NR, m/s Mean of 3 walks with/without FES	Sig ↑ with FES (group 1) ($P=.06$) *Sig diff	Sig ↑ with FES (group 1) (6wk) ($P=.06$)	*Sig effect with FES	NR	NR	NR	NR

Article	Short Walking Performance Tests Test Used Pace/Measured in Other Details	Orthotic Effect		Therapeutic Effect	Long Walking Performance Tests Test Used Measured in Other Details	Orthotic Effect		Therapeutic Effect (8–20wk)
		Initial	Ongoing (up to 20wk)			Initial	Ongoing (up to 20wk)	
		with FES (group 2)						
Van der Linden et al ⁴⁰	6MWT SSWS, m/s 6 walks with, 6 walks without FES, barefoot	Sig ↑ with FES ($P=.039$)	NR	NR	NR	NR	NR	NR
Van der Linden et al ⁴¹	10MWT Pace NR, Mean of 2 walks with and without FES	Sig ↑ with FES ($P=.006$)	Sig ↑ with FES at 6 and 12wk ($P=.006$)	↑ at 12wk (8.2%, Cohen $d<.29$)	2minWT Distance walked (m)	Sig ↑ with FES ($P=.002$)	Sig ↑ with FES at 6 and 12wk ($P=.002$)	↑ at 12wk (%), Cohen $d<.29$)

480

481 **Table 4: Methodological quality assessment using the Effective Public Health Practice Project (EPHPP) tool**

Study	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawals	Global Rating
Barr et al ²⁵	Moderate	Moderate	N/A	Weak	Weak	Strong	Weak
Barrett et al ²⁶	Strong	Moderate	Strong	Weak	Strong	Strong	Moderate
Barrett and Taylor ²⁷	Moderate	Moderate	N/A	Weak	Strong	Strong	Moderate
Downing et al ²⁸	Moderate	Moderate	N/A	Weak	Strong	Strong	Moderate

Study	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawals	Global Rating
Hausmann et al ²⁹	Moderate	Weak	N/A	Weak	Strong	Weak	Weak
Mayer et al ³⁰	Moderate	Moderate	Weak	Weak	Weak	Strong	Weak
Miller et al 2014 ³¹	Moderate	Moderate	N/A	Weak	Weak	Strong	Weak
Miller et al 2015 ³²	Moderate	Moderate	Strong	Weak	Weak	Strong	Weak
Paul et al ³³	Moderate	Moderate	N/A	Weak	Weak	N/A	Weak
Scott et al ³⁴	Moderate	Moderate	N/A	Weak	Strong	N/A	Moderate
Sheffler et al ³⁵	Weak	Weak	N/A	Weak	Strong	Strong	Weak
Sheffler et al ³⁶	Moderate	Moderate	N/A	Weak	Strong	Moderate	Moderate
Stein et al ³⁷	Moderate	Moderate	N/A	Weak	Strong	Strong	Moderate
Street et al ³⁸	Moderate	Moderate	N/A	Weak	Strong	Moderate	Moderate
Taylor et al ⁴²	Moderate	Moderate	Weak	Weak	Moderate	Strong	Moderate
Taylor et al ¹²	Moderate	Moderate	N/A	Weak	Strong	Strong	Moderate
Taylor et al ³⁹	Moderate	Strong	Strong	Weak	Strong	Strong	Moderate
Taylor et al ¹³	Moderate	Moderate	N/A	Weak	Strong	Strong	Moderate
Van der Linden et al ⁴⁰	Moderate	Moderate	N/A	Weak	Weak	Strong	Weak
Van der Linden et al ⁴¹	Moderate	Moderate	N/A	Weak	Strong	Strong	Moderate

483 **Table 5: Initial and ongoing orthotic and therapeutic effects for combined short walking performance tests** (*ft/s converted
484 to m/s where required, + no FES OFF data reported)

Study	Gait Speed for Combined Short Walking Performance Tests (m/s)*					
	Initial Orthotic		Ongoing Orthotic		Therapeutic	
	No FES	FES	No FES	FES	No FES (Baseline)	No FES
Barr et al ²⁵	1.18±0.17 (11)	1.17±0.17 (11)	1.20±0.19 (11)	1.25±0.19 (11)	1.18±0.17 (11)	1.20±0.19 (11)
Barrett et al ²⁶	0.79±0.16 (20)	0.79±0.15 (20)	0.73±0.16 (20)	0.80±0.16 (20)	0.79±0.16 (20)	0.73±0.16 (20)
Downing et al ²⁸	0.46±0.17 (19)	0.56±0.13 (19)	NR	NR	NR	NR
Mayer et al ³⁰	0.56±0.15 (20)	0.55±0.17 (20)	NR	0.67±0.12 (20)	NR	NR
Scott et al ³⁴	0.79±0.25 (11)	0.83±0.25 (11)	NR	NR	NR	NR
Sheffler et al ³⁶	NR	NR	0.83±0.16 (11)	0.82±0.21 (11)	NR	NR
Stein et al ³⁷	0.78±0.13 (30)	0.81±0.15 (30)	0.82±0.15 (30)	0.88±0.14 (30)	0.78±0.13 (30)	0.82±0.15 (30)
Street et al ³⁸	0.72±0.05 (153)	0.79±0.05 (153)	0.72±0.06 (153)	0.82±0.05 (153)	0.72±0.05 (153)	0.72±0.06 (153)
Taylor et al ⁴²	0.52±0.10 (21)	0.54±0.10 (21)	0.48±0.10 (21)	0.57±0.11 (21)	0.52±0.10 (21)	0.48±0.10 (21)
Taylor et al ¹²	0.49±0.09 (39)	0.55±0.10 (39)	NR	NR	NR	NR
Van der Linden et al ⁴⁰	0.74±0.20 (20)	0.80±0.21 (20)	NR	NR	NR	NR

Study	Gait Speed for Combined Short Walking Performance Tests (m/s)*					
	Initial Orthotic		Ongoing Orthotic		Therapeutic	
	No FES	FES	No FES	FES	No FES (Baseline)	No FES
Van der Linden et al ⁴¹	0.79±0.15 (9)	0.86±0.12 (9)	0.89±0.15 (9)	0.94±0.16 (9)	0.79±0.15 (9)	0.89±0.15 (9)
Average results from available data	0.69±0.03 (353)	0.74±0.03 (353)	0.74±0.04 (255)	0.82±0.04 (255)	0.74±0.04 (244)	0.74±0.04 (244)

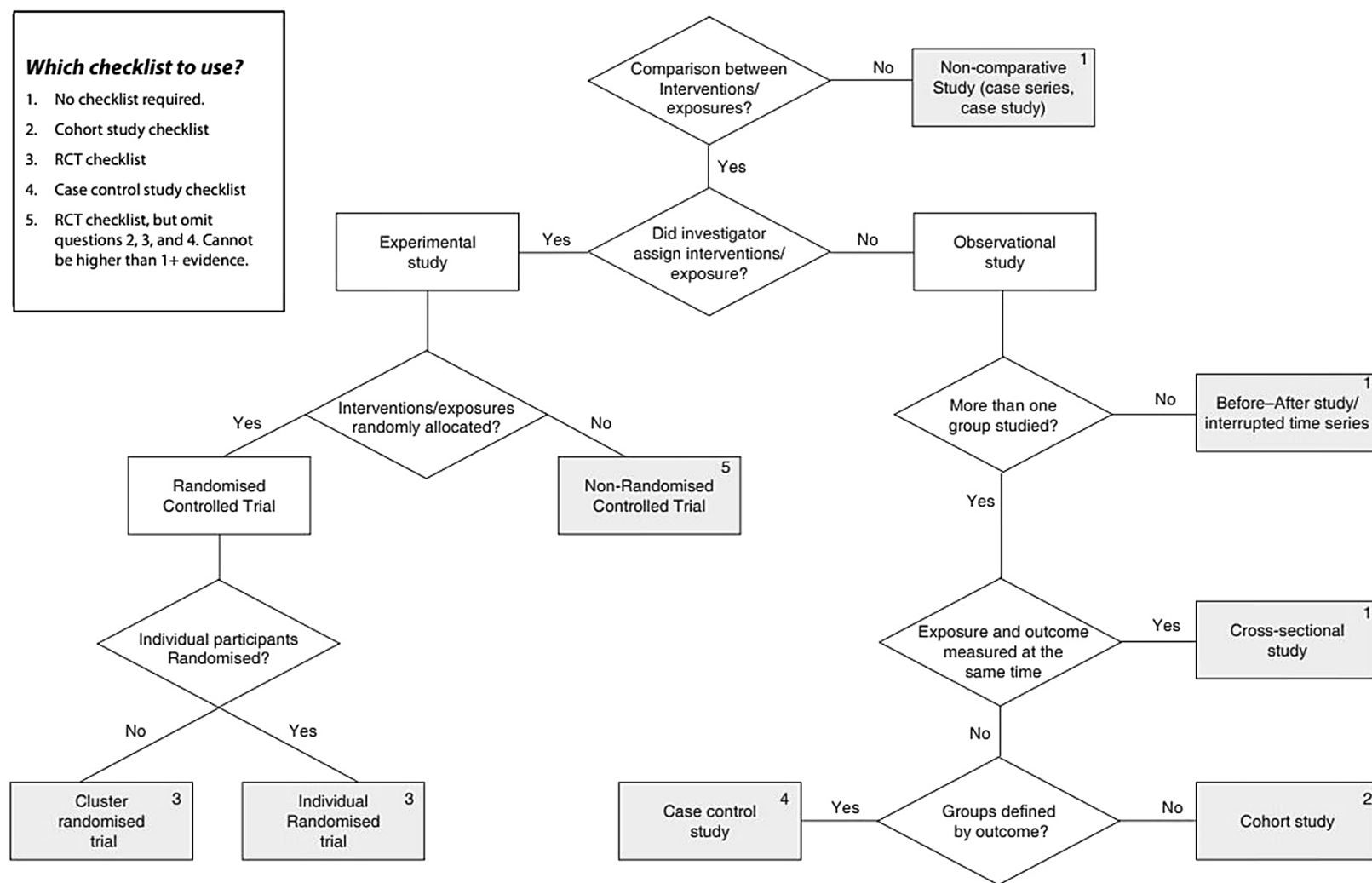
485

486 **Table 6: Initial and ongoing orthotic and therapeutic effects for combined long walking performance tests**

Study	Gait Speed for Combined Long Walking Performance Tests (m/s)*					
	Initial Orthotic		Ongoing Orthotic		Therapeutic	
	No FES	FES	No FES	FES	No FES (Baseline)	No FES
Barrett et al ²⁶	0.55±0.11 (20)	NR	0.62±0.14 (20)	0.69±0.15 (20)	0.55±0.11 (20)	0.62±0.14 (20)
Mayer et al ³⁰	0.60±0.12 (20)	0.59±0.23 (20)	NR	0.66±0.11 (20)	NR	NR
Scott et al ³⁴	0.82±0.11 (8)	0.80±0.09 (8)	NR	NR	NR	NR
Stein et al ³⁷	0.53±0.08 (32)	0.54±0.08 (32)	0.58±0.10 (32)	0.61±0.09 (32)	0.53±0.08 (32)	0.58±0.10 (32)
Van der Linden et al ⁴¹	0.84±0.15 (9)	0.87±0.14 (9)	0.88±0.17 (9)	0.92±0.19 (9)	0.84±0.15 (9)	0.88±0.17 (9)
Average results from available data	0.61±0.05 (89)	0.63±0.05 (69)	0.64±0.07 (61)	0.68±0.05 (81)	0.58±0.06 (61)	0.64±0.07 (61)

487

Algorithm for classifying study design for questions of effectiveness



488

489 **Figure 1: SIGN algorithm for classifying study design**

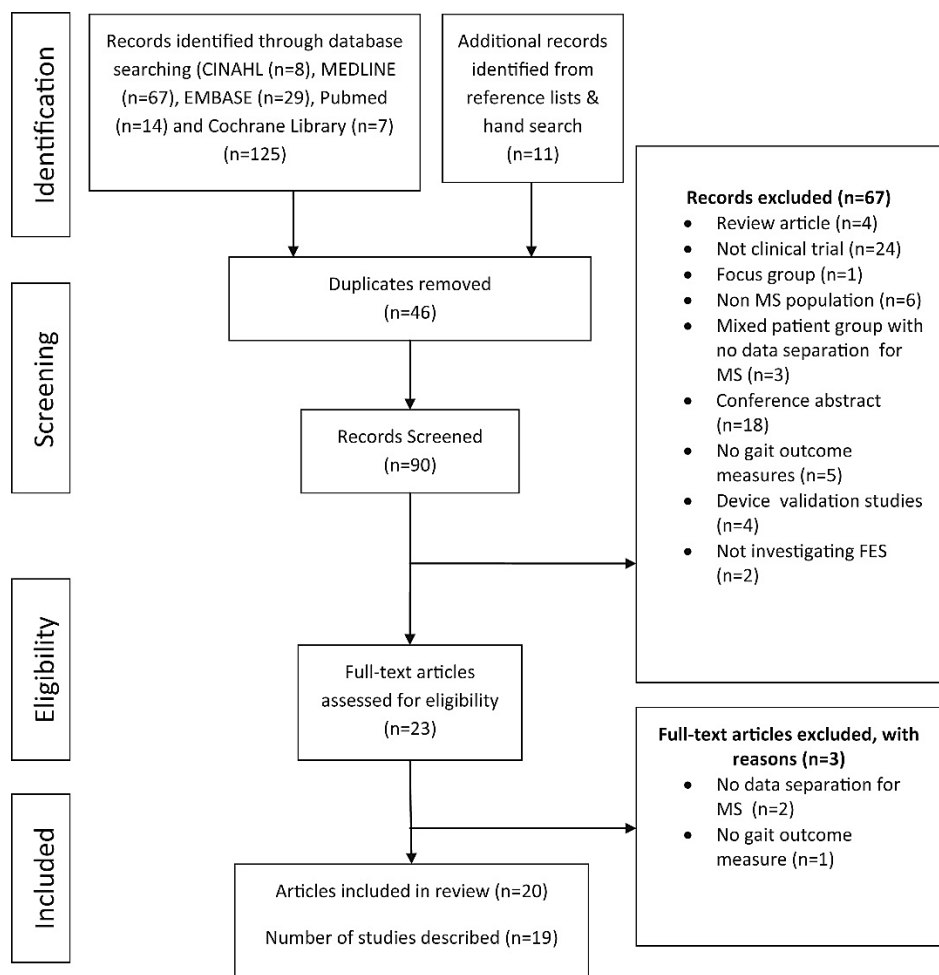


Figure 2: PRISMA flowchart demonstrating identification process for systematic review